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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	10

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/254,617	Applicant(s) MALLET ET AL	
	Examiner Anne- Marie Baker	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

The response filed March 8, 2001 (Paper No. 8) has been entered. Applicants' election with traverse of Group I, Claims 26-38 and 51 in Paper No. 8 is acknowledged. The traversal is on the grounds that the unity of invention standard from the PCT rules must be applied since this case was filed under 35 U.S.C. 371. Moreover, Applicants argue that a single general inventive concept exists. The Examiner agrees. Thus, Claims 26-38 and 51 are rejoined with Claims 39-50. Claims 26-51 are hereby rejoined and fully examined for patentability under 37 CFR 1.104.

Since all claims have been rejoined, the restriction requirement made in Paper No. 6 is hereby withdrawn.

Claims 26-51 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-35, 37-42, 44, 45,49, 50, and 51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating amyotrophic lateral sclerosis (ALS) comprising systemic administration of a pharmaceutical composition comprising an adenoviral vector encoding a neurotrophic factor and a pharmaceutical composition comprising two adenoviral vectors encoding two neurotrophic factors, does not reasonably provide enablement for a method of treating ALS by administering any type of vector encoding a neurotrophic factor or a pharmaceutical composition comprising

any type of vector encoding a neurotrophic factor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification fails to provide an enabling disclosure for the systemic administration of any type of vector encoding a neurotrophic factor, other than an adenoviral vector, because the specification does not provide specific guidance for producing a therapeutic effect by the systemic administration of another type of vector, such as a plasmid vector. The specification contemplates using a plasmid vector in the same manner as the adenoviral vectors described in the working examples. However, gene therapy is not routinely successful and different vectors exhibit different modes of action and different effects in an unpredictable manner. Therefore, the disclosure must enable the full scope of the claimed methods with specific guidance. However, the specification does not provide any guidance as to the level of gene expression required, the number of transfected cells needed, when the neurotrophic factor gene should be expressed, or the frequency of administration of the neurotrophic factor-encoding gene required to treat ALS. Furthermore, the specification fails to provide an enabling disclosure for gene therapy using any type of gene therapy vector, other than an adenoviral vector. At the time the application was filed, the art of administering any type of genetic expression vector to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable. The NIH *ad hoc* committee to assess the current status and promise of gene therapy reported in December 1995 that "clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims...," and that "significant problems remain in all basic aspects of gene therapy" (Orkin and Motulsky, p. 1). In a review article published in Scientific American in June 1997, Theodore Friedmann discusses the technical barriers which have so far prevented successful gene therapy, and states "So far, however, no approach has definitively improved the health of a single one of the

more than 2,000 patients who have enrolled in gene therapy trials worldwide" (p. 96). In a review article published in Nature in September 1997, Inder Verma states "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239). Thus, absent any showing that vectors other than adenoviral vectors could be used to produce the intended therapeutic effect in an immunocompetent animal, such as a human, the full scope of the claims are not enabled by the disclosure.

In view of the quantity of experimentation necessary to determine appropriate parameters for the claimed method of treatment using vectors other than adenoviral vectors, and further given the limited guidance in the specification, the limited working examples directed to in vivo gene therapy, the broad scope of the claims, and the unpredictable and undeveloped state of the art with respect to gene therapy at the time of the invention, undue experimentation would have been required for one skilled in the art to practice the claimed method over the full scope and to use the full scope of the claimed compositions.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 26-51 are indefinite in their recitation of "expression system" because the use of the term in the claims is in direct conflict with the definition of the term in the specification. The specification defines the term "expression system" at page 7, lines 4-17, as any construct allowing the in vivo expression of a nucleic acid coding for a neurotrophic factor. As used in the art, the term construct refers to a particular arrangement of genetic elements in a nucleic acid. However, this term is not synonymous with the term

"vector" and does not encompass vectors per se. In the claims, the term "expression system" is used synonymously with the term "vector" or to encompass the term "vector". For example, in Claim 41 the expression system is a vector and in Claim 42 the vectors are viral vectors and in Claim 43 the vectors are adenovirus. Given their plain meaning, one of skill in the art would not understand the term "construct" to include **vectors** of which those constructs may be a part. The metes and bounds of the claim are not clearly set forth.

Claim 29 is indefinite in its recitation of "comprising two nucleic acids" because it is unclear how a single expression cassette can comprise "two nucleic acids".

Claim 49 is indefinite in its recitation of "in intravenously injectable" because the sentence is incomplete.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 39-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haase et al. (1997).

The claims are directed to a pharmaceutical composition comprising an expression system for two neurotrophic factors.

Haase et al. (1997) disclose adenoviral vectors encoding neurotrophin-3 (NT-3) and ciliary neurotrophic factor (CNTF). The reference further discloses the use of these two adenoviral vectors together for intramuscular administration to *pmn* mice. Thus, the reference implicitly discloses a pharmaceutical

composition comprising both adenoviral vectors for simultaneous administration to the mice. Further, given that the reference discusses the usefulness of numerous other neurotrophic factors at page 429, column 1, paragraph 2, particularly the successful use of CNTF and BDNF in *wobbler* mice, one of skill in the art would have been motivated to construct other adenoviral vectors encoding other neurotrophic factors, particularly BDNF, and to use these vectors in combination with each other, thereby providing motivation to prepare other pharmaceutical compositions comprising two or more adenoviral vectors encoding two or more different neurotrophic factors.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

This rejection may be overcome by providing an English translation of the French priority document 96/11186, filing date September 13, 1996 and demonstrating that the claimed pharmaceutical compositions are disclosed therein.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Kay Pinkney, whose telephone number is (703) 305-3553.

Anne-Marie Baker, Ph.D.

Anne-Marie Baker
ANNE-MARIE BAKER
PATENT EXAMINER